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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,989	05/29/2001	Wilfred Wayne Lautt	14430.0001USWO	7861

23552 7590 01/21/2010

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EXAMINER	
LOVE, TREVOR M	

ART UNIT	PAPER NUMBER
1611	

MAIL DATE	DELIVERY MODE
01/21/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/806,989	LAUTT, WILFRED WAYNE	
	Examiner	Art Unit	
	TREVOR M. LOVE	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/17/2008, 06/05/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-20 are cancelled.

Claim 21 is currently amended.

Claims 21-25 are pending and currently under consideration.

Acknowledgement is made to Applicant's response filed 06/05/2009.

Acknowledgement is made to Applicant's Power of Attorney accepted 08/27/2009.

Withdrawn Rejections and/or Objections

The rejection of claims 21-25 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of Applicant's amendment to claim 21.

The rejection of claims 1-3 and 19 under 103(a) as being unpatentable over Chwalisz et al. (US Patent Application Publication No. 2001/0056068, filed Mar. 4, 1998), in view of Herfindal et al. (Herfindal et al. Clinical Pharmacy & Therapeutics. 1992, Chapter 17, pages 307-331, especially page 308, col. 1, 2nd full para. to col. 2, 2nd para.) is withdrawn in view of Applicant's cancellation of claims 1-3 and 19.

Claim Rejections - 35 USC § 103

Maintained

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 21-25 are rejected under 103(a) as being unpatentable over Chwalisz et al. (US Patent Application Publication No. 2001/0056068, filed Mar. 4, 1998), in view of Herfindal et al. (Herfindal et al. Clinical Pharmacy & Therapeutics. 1992, Chapter 17, pages 307-331, especially page 308, col. 1, 2nd full para. to col. 2, 2nd para.). This rejection is maintained.

Chwalisz teaches methods for control, management, treatment and prevention of various conditions related to nitric oxide deficiency, including hypertension, cardiovascular disease, osteoporosis, diabetes, male impotence, urinary incontinence, and uterine contractility disorders by administering citrulline or a citrulline analogue, optionally in combination with other enhancing or modulating agents (abstract). Chwalisz teaches that nitrovasodilators such as nitroglycerin and sodium nitroprusside (SNP) inhibit vascular smooth muscle contractility to produce vascular relaxation and to reduce vascular tone and that these compounds release nitric oxide (acting as nitric oxide donors) either spontaneously (e.g. SNP) or after metabolic conversion (e.g. nitroglycerin; para. 0016, lines 1-4). Chwalisz teaches that endogenous nitric oxide levels can also be raised by L-arginine (nitric oxide substrate) treatment (para. 0016). Chwalisz states that since nitric oxide is involved in numerous pathophysiological processes, it is

theoretically possible to overcome some nitric oxide deficiency conditions with NO donors (page 2, last line to page 3, first three lines). Chwalisz teaches that the NO donors are mostly nonspecific and tolerance may develop which limits their use (page 3, col. 1, first para., beginning at line 3). Chwalisz teaches NO donors, including nitroglycerin, and L-arginine analogues (e.g. NG-nitro-L-arginine methyl ester or L-NAME), glyceryl trinitrate, sodium nitroprusside, SIN-1, isosorbid mononitrate, and isosorbide dinitrate (page 3, col. 1, first para., beginning at line 3; and page 8, para. 0090).

Chwalisz does not directly teach the specific method steps recited in claim 21.

Herfindal teaches that diabetes is comprised of two major clinical conditions: type II maturity-onset, which represents about 80% of diabetics, and type 1 juvenile-onset, which represents only 15 to 20% of diabetic cases (page 308, col. 1, 2nd full para. to col. 2, first col.). Herfindal states that most type II diabetics retain some pancreatic function and may be controlled by diet plus oral hypoglycemic drugs even though insulin may be required in 20 to 30% of type cases, while type I diabetics require insulin to sustain life since they have no pancreatic function (page 308, col. 1, 2nd full para. to col. 2, first para.).

It would have been obvious to a person of skill in the art at the time the invention was made to treat a patient with diabetes mellitus, including a patient with Type II diabetes, with a therapeutically effective amount of a therapeutic nitric oxide donor compound, either singly or in combination (e.g. nitroprusside and/or SIN-1), to control the symptoms of diabetes which include insulin resistance. One would have been motivated to do so since Chwalisz teaches a method of treating diabetes mellitus comprising administering an effective amount of a nitric oxide donor compound (e.g. nitroprusside or SIN-1) which may be administered separately or in

combination. There would be a reasonable expectation of success in treating a patient with Type II diabetes, whose symptoms include insulin resistance, as taught by Herfindal with a non-insulin type NO donor drug (e.g. SIN-1) as taught by Chwalisz since Type II diabetes mellitus is routinely treated with non-insulin drugs (e.g. nitroprusside or SIN-1) and both Chwalisz and Herfindal are directed to the treatment of diabetes.

Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat a patient with type II diabetes with a combination of two nitric oxide donor compounds (e.g. SIN-1 and sodium nitroprusside), for additive effect, in controlling the symptoms of diabetes by administering said two nitric oxide donor compounds (e.g. SIN-1 and sodium nitroprusside) to the patient via any suitable pharmaceutical means, including administering one of the nitric oxide donors in a unit dosage injectable formulation comprising an effective amount of the drug (e.g. sodium nitroprusside) and sequentially administering an oral dosage formulation comprising an effective amount of the second nitric oxide), depending on the storage stability of the dosage form, the oral bioavailability of the drug and the pharmaceutical suitability of the drug for injectable/oral use, as well as the required dose amount, which would vary depending on patient factors as body weight and oral tolerance to the specific drug(s). One would have been motivated to do so because Chwalisz teaches nitric oxide donor compounds can be administered by unit dosage injectable formulation or oral dosage forms (0114; 0116-0117) and that combination of agents can be employed either continuously or sequentially (para. 0119, last two lines). Also, Chwalisz teaches that NO donors are mostly nonspecific and that tolerance may develop with said drugs which limit their use and therefore one would expect to successfully combine two nitric oxide donor compounds, wherein the first

compound is administered in a unit dosage injectable formulation comprising an effective amount of nitric oxide donor for increasing insulin sensitivity and subsequently administering an oral dosage formulation comprising an effective amount of a nitric donor for maintaining insulin sensitivity for additive effect. It is routine to administer a bolus dose of a drug via a unit dosage injectable formulation, for its immediate therapeutic effect, followed by the administration of the same or different drug via oral dosage form in patients who require long-term treatment. It is noted that Type II diabetes mellitus is a chronic condition. In addition, the dosage form and the route of administration of drugs are routinely manipulated to optimize therapeutic effects and minimize side effects depending on the pharmaceutical characteristics of the specific drug since some drugs may be better tolerated when administered by injection (e.g. drugs that cause upset stomach) while others may be better tolerated by patients when administered by mouth (e.g. drugs that cause pain upon injection).

It is noted that the prior art teaches the same instantly claimed nitric oxide donor compounds (e.g. nitroprusside and SIN-1) to treat the same population (diabetes mellitus, which suffer from insulin resistance, and therefore are in need of increasing insulin sensitivity) and therefore one would reasonably expect that administration of the same drug to the same population as taught by the prior art would also have the same therapeutic effects as claimed, including increasing insulin sensitivity in a patient.

Regarding claim 25, Chwalisz teaches nitric oxide donors are preferably administered at least once daily (para. 0119) and also teaches tablet and capsule dosage forms comprising nitric oxide donors (para. 0116). Thus, it is the examiner's position that it would have been obvious to a person of skill in the art at the time the invention was made to administer more than one tablet

or capsule comprising a nitric oxide donor as taught by the prior depending on the required dose of the nitric oxide donor, which would reasonably vary depending on patients factors such as age, body weight, the specific disease condition, and severity of the disease.

Response to Arguments

Applicant argues in the remarks filed 06/05/2009 that the pending claims recite a method of "increasing insulin sensitivity in a subject in need thereof" and administering "an effective amount of a nitric oxide donor or nitric oxide agonist for increasing insulin sensitivity in said subject". Applicant argues that the art cited by the Examiner fails to make a connection between a nitric oxide deficiency and insulin sensitivity. Applicant's arguments have been fully considered and are not found persuasive. Specifically, Chwalisz teaches that diabetes is associated with reduced nitric oxide amounts, wherein reduced nitric oxide is treated by the administration of a nitric oxide agonist or donor. Further, Herfindal teaches that diabetes is associated with increased insulin resistance (see Herfindal, page 308, first column third paragraph). Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made that the administration of a nitric oxide agonist or donor would treat diabetes including the associated insulin resistance and one of ordinary skill in the art would readily recognize that alleviating insulin resistance would increase insulin sensitivity. Therefore, it is prima facie obvious that treatment of diabetes with nitric oxide agonists or donors would reduces associated insulin resistivity(i.e. increases insulin sensitivity). Applicant is reminded that "A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton."KSR, 550 U.S. at __, 82 USPQ2d at 1397. "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle."Id.

Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ."Id. at _ , 82 USPQ2d at 1396. The idea that one of ordinary skill in the art would not appreciate that the treatment of diabetes and associated insulin resistance and therefore, increasing insulin sensitivity makes little sense. Further, even assuming arguendo that one of ordinary skill in the art would not recognize that the treatment of diabetes and associated insulin resistance would increase insulin sensitivity, this would have necessarily occurred following the teachings of Chwalisz and Herfindal. As set forth above, Chwalisz and Herfindal teaches the same instantly claimed nitric oxide donor compounds (e.g. nitroprusside and SIN-1) to treat the same population (diabetes mellitus, which suffer from insulin resistance). Therefore, the administration of the same drug to the same patient population as taught by the prior art would necessarily increase insulin sensitivity in the patient. The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979).

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references and the rejection is maintained.

Conclusion

No claims allowed. All claims rejected. No claims objected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TREVOR M. LOVE whose telephone number is (571)270-5259. The examiner can normally be reached on Monday-Thursday 7:30-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TL

/David J Blanchard/
Primary Examiner, Art Unit 1643